# CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH SEVERE MENTAL ILLNESS

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# 1. Acknowledgements

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## 2. List of papers

**Paper I.**

Birkenaes AB, Søgaard AJ, Engh JA, Jonsdottir H, Ringen PA, Vaskinn A, Friis S, Sundet K, Opjordsmoen S, Andreassen OA. Socio-demographic characteristics and cardiovascular risk factors in patients with severe mental disorders compared with the general population. J Clin Psychiatry 2006;67(3):425-433.

**Paper II.**

Birkenaes AB, Opjordsmoen S, Brunborg C, Engh JA, Jonsdottir H, Ringen PA, Simonsen C, Vaskinn A, Birkeland KI, Friis S, Sundet K, Andreassen OA. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia. A comparative study. J Clin Psychiatry 2007;68(6):917-923.

**Paper III.**

Birkenaes AB, Birkeland KI, Engh JA, Jonsdottir H, Ringen PA, Færden A, Friis S, Opjordsmoen S, Andreassen OA**.** Dyslipidemia independent of body mass in antipsychotic treated patients under real life conditions. J Clin Psychopharmacol 2008;28(2):132-137.

**Paper IV.**

Birkenaes AB, Birkeland KI, Friis S, Opjordsmoen S, Andreassen OA. Dysregulation of metabolic hormones following antipsychotic treatment in a naturalistic sample of patients with severe mental illness. Submitted.

# 3. Summary of Study

Individuals with severe mental illness (SMI) have much higher mortality rates from somatic causes than the general population, with life expectancies reduced by 10-30 years. The excess premature mortality has been shown to increase throughout the last decades, and is expected to continue rising well into the new millennium. As in the general population, cardiovascular disease (CVD) is the leading cause of death in patients with schizophrenia, bipolar disorder and severe depression, and contrary to the overall situation in western society, mortality from CVD in psychiatric patients is not declining. Previous studies have linked the increased cardiovascular risk in psychiatric patients to poor life-style and inadequate health services. Others have indicated that individuals with SMI may have a specific vulnerability for metabolic disturbances, intrinsic to the disease state itself. Finally, recent investigations have payed much attention to the liability of antipsychotics (APs) to cause weight gain and other metabolic side effects. However, results have been non-conclusive, and the underlying mechanisms linking psychiatric and somatic disorders remain to be elucidated.

The main object of the present studies was to gain more knowledge about CVD risk factors in patients with severe psychiatric disorders, with particular emphasis on the metabolic side effects of AP treatment. The first aim was to investigate the prevalence of known CVD risk factors in a representative sample of Norwegian patients, as compared with an age-matched reference group from the general population, and to determine the role of life style, using socio-demographic factors as a surrogate measure. The second aim was to assess the role of diagnosis, psychiatric symptom severity level, and the overall use of psychopharmacological treatment, by comparing CVD risk in subjects with schizophrenia and bipolar disorder. The third aim was to investigate whether increased levels of cardio-metabolic risk parameters were associated with the commonly used AP agent olanzapine (OLZ), and how these were related to adiposity. The fourth aim was to investigate whether dysregulation of metabolic hormones was found in OLZ treated subjects, independent of body mass and body composition.

This report is based upon naturalistic data from the cross-sectional part of the Thematically Organized Psychosis Research (TOP) Study, carried out in joint collaboration between the University and University Hospitals of Oslo. Eligible patients were all those (1) registered in the psychiatric services of one of the University Hospitals in Oslo; (2) aged 18 to 65 years; (3) meeting DSM-IV criteria for a major psychotic illness; and (4) being able and willing to give informed, written consent of participation. From October 2002 through July 2006 a total of 414 patients were included, from all health care sectors of Oslo. For the different sub-studies, subjects from this main sample were selected according to the objectives of that particular investigation. Reference data were based upon the 2000/2001 Oslo Health Study (HUBRO), including a total of 18,770 individuals from the general population of Oslo.

Most known CVD risk factors were found to be approximately twice as prevalent in the study sample as in the general population, and young patients had the highest relative increase in risk. Differences in risk profiles between patients and references could not be explained by sociodemographic factors alone. Subjects with schizophrenia and bipolar disorder had approximately the same level of CVD risk factors. AP treatment with OLZ was associated with dyslipidemia, insulin resistance and increased levels of circulating leptin, independent of body mass and body composition. Women seemed to be particularly at risk for dysregulation of metabolism following OLZ treatment.

In conclusion, cardio-metabolic risk was shown to be alarmingly high among subjects with SMI, independent of sociodemographic background, diagnoses, and psychiatric symptom severity. Dyslipidemia and insulin resistance were associated with specific AP treatment and could not be explained by weight gain alone.

# 4. Abbreviations

| | |
|---|---|
| AHA | American Heart Association |
| AMPK | Adenosine monophosphate-activated protein kinase |
| AP | Antipsychotic |
| BMI | Body mass index (weight in kg divided by the square of the height in m) |
| BP | Blood pressure |
| CATIE | the Clinical Antipsychotic Trials of Intervention Effectiveness Study |
| CLZ | Clozapine |
| CVD | Cardiovascular disease |
| DSM-IV | Diagnostic and Statistic Manual of Mental Disorders, $4^{th}$ edition |
| FGA | First generation antipsychotic |
| FPG | Fasting plasma glucose |
| GAF | Global Assessment of Functioning |
| HDL-C | High density lipoprotein cholesterol |
| HOMA-IR | Homeostasis Model Assessment of Insulin Resistance |
| HPA | Hypothalamus-pituitary-adrenal |
| H1R | $H_1$ histamine receptor |
| HUBRO | the 2000/2001 Oslo Health Study |
| IDS | Inventory of Depressive Symptoms |
| IQ | Intelligence Coefficient |
| LDL-C | Low density lipoprotein cholesterol |
| MetS | Metabolic syndrome |
| NCEP ATP III | National Cholesterol Education Program, Adult Treatment Panel III |
| NHLBI | National Heart, Lung, and Blood Institute |
| NIMH | The National Institute of Mental Health |
| NOS | Not otherwise specified |
| OLZ | Olanzapine |
| PANSS | Positive and Negative Symptoms of Schizophrenia |
| SCID-I | Structured Interview for the DSM-IV Axis I Disorders |

| | |
|---|---|
| SGA | Second generation antipsychotic |
| SHBG | Sex hormone-binding globulin |
| SMI | Severe mental illness |
| SMR | Standard mortality rate (calculated by dividing the observed mortality of a cohort by the expected mortality of an age-and gender-matched cohort of the general population) |
| TC | Total cholesterol |
| TGs | Triglycerides |
| TOP | Thematically Organized Psychosis Study |
| U-600 | Ulleval 600 (part of the TOP Study) |

# 5. Introduction

## 5.1. Increased rates and causes of mortality in severe mental illness

### 5.1.1. The pre-neuroleptic era

Since the 17th century, there have been clinical reports in Western Europe on increased mortality among the mentally ill (Graunt, 1662). Pre-second world war psychiatry had no efficient treatment for schizophrenia or severe affective disorder. Patients, who could not be cared for by their families, were confined to lunatic asylums, under conditions that we, today, find deleterious and inhumane.

During the first part of last century, two large Scandinavian studies were conducted on death rates and causes of death in the asylums (Ödegard, 1936; Alström, 1942). The authors made use of standardised mortality ratios (SMRs), calculated by dividing the observed mortality of a cohort by the expected mortality of an age- and gender-matched cohort of the general population, to measure differences in mortality. Both authors reported significantly elevated mortality among schizophrenia subjects, with SMRs between 2.1 and 4.0. The main causes of death were found to be tuberculosis and pneumonia, ascribed to the conditions of overcrowding, malnutrition, and poor hygienic conditions in the large institutions. A little later, Bleuler (1950) attributed most of the excess deaths in schizophrenia to "the indirect consequences of psychosis: refusal of food, intentional and unintentional injuries, suicide, tuberculosis and other diseases resulting from unhygienic ways of life".

### 5.1.2. The post-neuroleptic era

After the Second World War, Western psychiatry was gradually transformed by new insights into the aetiology of mental disease and a more humane approach. Treatment was revolutionized by the introduction of drugs that provided efficient symptom control, such as lithium in 1948, chlorpromazine in 1952, and amitriptyline in 1960. From 1970 onwards,

deinstitutionalization gradually took place and the asylums were substituted by community based care.

However, excess death rates among the mentally ill prevailed. In a meta-analysis of mortality studies among patients with schizophrenia between 1952 and 1995, Brown (1997) found that death rates were increased in every report included in the analysis, with an aggregate SMR of 1.5. These findings were replicated one year later in the systematic meta-analysis by Harris & Barraclough (1998). Follow-up studies on schizophrenia cohorts conducted more recently, have indicated an increase in the overmortality among these patients (Brown *et al*, 2000; Ösby *et al,* 2000[a]; Ösby *et al,* 2000[b]). This tendency was confirmed in a recently published meta-analysis covering 37 studies from 25 countries, published between 1980 and 2006. In this study, the median all-cause SMR was 2.6, and the authors found that from 1970 through 1999, the differential mortality gap between schizophrenia patients and the general population had increased in a linear fashion (Saha *et al*, 2007).

Although less comprehensive, parallel investigations have been performed on death rates in bipolar disorder, yielding similar results. In the meta-analysis by Harris & Barraclough (1998), and in two later follow-up studies by Angst *et al* (2000) and Ösby *et al* (2001) the reported SMRs in this group of patients was between 1.6 and 2.6.

Poverty and infectious diseases are no longer major health problems in Western Europe, and causes of death in the mentally ill have shifted with that of the general population. In the cohorts from second part of last century examined by Brown (1997), Harris & Barraclough (1998), Brown (2000), and Ösby *et al* (2000), the authors estimated that approximately 40 % of the excess deaths in schizophrenia were due to suicide and unspecified violence, while 60 % were due to natural causes. Natural deaths were caused by the same broad spectrum of conditions as in the general population, and the largest single cause of death was CVD, in both males and females. The overall risk for cardiovascular death in schizophrenia was about 2-fold, and thus moderately increased, as compared to a 15-20 fold risk for suicide, but CVD still accounted for the largest total number of excess

deaths. In addition, the risk of cardiovascular death was clearly increasing throughout the study period (Ösby, 2000). For bipolar disorder, Harris & Barraclough (1998), Ösby (2001), and Angst *et al* (2002), found the same pattern of mortality causes, with circulatory diseases being responsible for the highest number of excess deaths, followed by suicide.

### 5.1.3. The last decennium

Since 1995, major improvements in the pharmacotherapy of mental illness have occurred with the introduction of second generation antipsychotics (SGAs), along with new antidepressants and mood-stabilizers. Accordingly, adherence to treatment has been facilitated, and many patients have been helped to a better integration in society. Despite these progresses, mortality rates in psychiatric populations remain exceedingly high. In a recent study across eight American states, Colton & Manderscheid (2006) showed that life expectancy for people with SMI was 20-30 years shorter than for the general population, with cardiovascular disease being the leading cause of death. In accordance with this, Enger *et al* (2004) reported that in the USA between 1995 and 1999, treated schizophrenia outpatients had a 5-fold increased risk of death by myocardial infarction. The situation seems to be about the same in Western Europe. Thus, a population based study, including almost all individuals with psychosis or severe mood disorder in the United Kingdom between 1987 and 2002, demonstrated a 3-fold increased risk of CVD death in patients below 50 years, and a 2-fold increased risk in patients above 50 years of age. (Osborn *et al,* 2007).

## 5.2. Causality factors

The precise origin of the raised vulnerability to CVD in the mentally ill has been sought for, but remains elusive and, most likely, cannot be attributed to a single mechanism. At present, most authors agree that the causality is multifactorial (Wildes *et al,* 2006), and the issue is being pursued along several lines of investigation.

### 5.2.1. Vulnerability to lifestyle hazards

According to a twin study of mortality in schizophrenia by Kendler (1986), the pattern of natural deaths in this disorder could not be due to the disease state alone, but was better explained by altered exposure to environmental risk factors. People with severe mental disorders are generally considered to have an illness-related vulnerability of adopting deleterious lifestyles (Ösby *et al,* 2000). Exposed to the general health threats of modern society, these patients are prone to excessive smoking, alcohol and drug abuse, poor diets, and lack of physical exercise (McCready *et al*, 2003; Davidson *et al*, 2001; Katon *et al*, 2003). Western society today is characterized by its "obesogenic" conditions, implicating that easy access to food and reduction in energy expenditure have made obesity and related disorders a major threat to public health (National Task Force, 2000; Bell *et al,* 2005). Allison *et al* (1999), and Homel *et al* (2001) were among the first to report on an increased prevalence of obesity in subjects with schizophrenia versus controls, also demonstrating that body mass in schizophrenia patients, females in particular, was dramatically increasing. This tendency has later been confirmed in several studies (McEvoy *et al*, 2005) and is now often referred to as "an epidemic within an epidemic" (Newcomer & Hennekens, 2007).

### 5.2.2. Insufficient medical care

Mortensen & Juel (1993) and Ösby *et al* (2000) ascribe the increase in "avoidable deaths" among schizophrenia patients to the rapid changes that have taken place within psychiatric care over the last 30 years, with long term inpatient units being replaced by outpatient treatment facilities, and a dramatic reduction in hospital beds assigned to this group of patients.

People with SMI frequently have an altered notion of somatic symptoms and a decreased ability to seek medical help. Unfortunately, somatic issues are often given low priority within the psychiatric services, while psychiatric patients get low priority within the somatic medical care system (Marder *et al*, 2004; Newcomer & Hennekens, 2007). Somatic disorders in patients with SMI are frequently not diagnosed and primary treatment neglected. Brown *et al* (2000) found that in the U.K., death rates of "avoidable" somatic

causes were nearly five times increased in schizophrenia, while Nasrallah *et al* (2006) reported that in the USA a large proportion of schizophrenia patients did not receive medical treatment for conditions such as diabetes (30 %), hypertension (62 %), and dyslipidemia (88 %). Also, secondary prevention is often inadequate. Based upon findings from a nation wide study on the quality of post myocardial infarction care, Druss *et al* (2007) concluded that follow-up treatment was deficient among patients with mental disorders, and could explain a substantial portion of the highly increased mortality found in this group. The decline in mortality from CVD in the general population during the last decades is considered to be largely an effect of improved diagnosis and treatment (Lichtenstein *et al,* 2006). There are thus strong indications that insufficient medical care is a major cause of the increasing overmortality seen in people with SMI (Newcomer & Hennekens, 2007).

### 5.2.3. Risk factors intrinsic to mental illness

There is, however, evidence that some CVD risk factors may be inherent to psychiatric illness itself. Long before the dawn of the "obesogenic society", metabolic disturbances were associated with SMI. Sir Henry Maudsley, in his "Pathology of the Mind", commented that "Diabetes is a disease which often shows itself in families in which insanity prevails" (Maudsley, 1879). During the first part of last century, specific alterations of energy metabolism were assumed to be an intrinsic factor of psychotic illness (Kraepelin, 1921; Bleuler, 1930). Dysregulation of vegetative functions was often linked to "body types" (Kretschmer, 1936), and studies were performed showing abnormal glucose tolerance in patients with "dementia preacox and manic depressive insanity" (Raphael & Parsons, 1921; Meduna, 1942; Langfeldt, 1952). Some imbalance in the sympathetic versus the para-sympathetic nervous system was presumed.

Recent studies seem to confirm that type 2 diabetes is more common in schizophrenia subjects (Henderson & Ettinger, 2002; Henderson, 2005; Ryan & Thakore, 2002; Thakore, 2005; Cohen *et al*, 2006), as well as in their otherwise healthy first-degree relatives (Mukherjee *et al*, 1989). There are also indications that drug-naïve individuals with

schizophrenia may have alterations in body composition, with larger amounts of visceral fat (Thakore *et al*, 2002), and more insulin resistance (Ryan *et al,* 2003), than matched controls. The reason for this, however, remains uncertain. One proposed hypothesis is that a common genetic vulnerability, or perinatal adversities, may dispose for insulin resistance as well as mental disorder. Alternatively, metabolic dysregulation is thought to be the result of disease specific stress resulting in chronic hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis.

Interestingly, a recent Finnish, register based study showed that the incidence of schizophrenia is substantially decreased in patients with type 1 diabetes, a finding which is not easily explained (Juvonen *et al,* 2007). The authors speculate that some factors associated with type 1 diabetes may modify the phenotype or the clinical picture of psychosis in the direction of affective disorder, but more research is clearly needed.

### 5.2.4. Adverse effects of treatment

The “cures” of the pre-neuroleptic era caused many deaths. According to Bleuler (1978), treatment accounted for 17 % of the total mortality in a schizophrenia cohort followed from 1942 to 1965. The mortality following leucotomy was from 1-18 %, varying among centres, dependent on the operation method, and skills of the operator (Swayze *et al*, 1995; Ögren *et al,* 2007). Insulin coma had a mortality of approximately 1%, and Cardiazole and ECT induced convulsions caused significant morbidity due to fractures, at least before the introduction of curare (Henderson & Gillespie, 1952). Not included in these crude figures, are the immense sufferings of the patients and their families in a period when no effective treatment was available.

With the introduction of chlorpromazine in 1952, the treatment of schizophrenia was revolutionized. However, improvement of psychosis often came at the price of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), sometimes causing more subjective suffering to patients than the disorder itself, and making adherence to treatment a great challenge. When the second generation antipsychotics (SGAs) became available in the

1990[ies], the risk of EPS and TD fell dramatically. In addition, according to some authors, the new drugs had better effect on negative symptoms, depression, and cognition (Davies *et al,* 2003). They were therefore enthusiastically welcomed for providing patients a better quality of life, and soon gained large access to the market.

However, with the new drugs, an old problem was exacerbated. Obesity as a result of pharmacological treatment had been noticed since the 1950[ies] (Planansky, 1958), but with the turn of the century, drug induced weight gain became a major obstacle in the treatment of severe mental disorders. In two meta-analyses addressing this issue, Allison *et al* (1999) and Allison & Casey (2001) concluded that most neuroleptics are potentially obesogenic, but that there are large differences between agents, with clozapine (CLZ) and olanzapine (OLZ) inducing most weight gain. These findings have been replicated in a multitude of other studies, causing growing concern about the obesity related, cardiovascular hazards associated with antipsychotic treatment (Meyer, 2001; American Diabetes Association, 2004, Nasrallah *et al,* 2004; Newcomer, 2005; Fenton & Chavez, 2006).

In addition to the hazards of EPS and weight gain, APs have been shown to increase the risk of serious ventricular arrhythmias. In one study on classical neuroleptics, Ray *et al* (2001) showed that patients prescribed moderate drug doses had large relative and absolute increases in the risk of sudden cardiac death, and that risk was even higher in users who already had CVD. There are indications that some SGAs also have proarrhythmic properties (sertindol, ziprazidone), but this is of little clinical importance (Drici *et al,* 1998; Lindström & Levander, 2006).

Up till now, it has not been possible to link any particular AP agent with increased CVD morbidity or mortality. Osborn *et al* (2007) concluded that the excess death rates found among mentally ill people in their study, could not wholly be explained by smoking or social deprivation. Nor could they be explained by the use of AP medication alone. None the less, patients prescribed APs seemed to be at even greater risk than those who were not prescribed these agents.

## 5.3. The metabolic syndrome

The association of obesity with metabolic disturbances and vascular disease is not new. By the year 1761, Morgagni had already discovered the co-occurrence of visceral fat accumulation, hypertension, abnormal metabolism and atherosclerosis (Enzi *et al,* 2003). The notion of a syndrome linking these parameters then went unnoticed until the 20th century, and was first really put on the medical agenda with the coining of the term "syndrome X" by Reaven (1988). Eventually, this rubric evolved into what is now generally known as the metabolic syndrome (MetS).

Primarily as a result of the increasing prevalence of obesity, diagnosis and management of the MetS has become an important medical challenge (Expert Panel of Detection, 2001; Bloomgarden, 2004; Eckel *et al,* 2005; Grundy *et al,* 2005). The MetS is best seen as a physiological change with clustering of interrelated metabolic risk factors for developing type 2 diabetes and CVD, as well as a variety of other disorders. Non-diabetic individuals with the syndrome have been shown to have a 2-3 fold increase in cardiovascular, and a 1.5-increase in all-cause mortality, after adjustments for age, smoking and blood cholesterol levels have been made. When the syndrome is complicated with diabetes, mortality is even higher (Hu *et al,* 2004).

However, the MetS has had its adversaries (Johnson & Weinstock, 2006). In a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes, Kahn *et al* (2005) argues that the syndrome is imprecisely defined, based on somewhat arbitrary cut-off values for the various risk factors. In addition, the authors emphasize that the symptoms associated with the syndrome have an uncertain common pathogenesis, and that there is doubt whether the cluster conveys risk beyond the risk associated with its individual components.

The International Diabetes Federation strongly argued against this critic (Zimmet & Alberti, 2005), and despite an ongoing debate, the concept has gained widespread use as a screening tool, mainly because it is low cost, easy to apply in clinical practice, and is generally considered to have high predictive value (Alberti, *et al,* 2005). Several expert groups have

attempted to set forth simple diagnostic criteria. There is now general agreement on the main *metabolic components* of the syndrome being elevated blood pressure, atherogenic dyslipidemia, and elevated plasma glucose (Grundy *et al,* 2005). There is, however, still discussion of whether abdominal obesity or insulin resistance may be the essential *cause* of the clustered metabolic disturbances (Balkau *et al*, 2002; Reaven, 2002). Although hypothesis on pathophysiology need to be harmonized, clarifying the relative importance of environmental exposure versus genetic vulnerability, the unifying point may be that insulin resistant individuals often have abnormal (upper-body) fat distribution, while adipose tissue in obese individuals often is insulin resistant. Thus, most current definitions have included the presumed *underlying risk factor* of abdominal obesity in the definition of the syndrome (Grundy *et al*, 2005).

It is important to emphasize that obesity in itself is only a weak risk mediator for type 2 diabetes and CVD. Metabolic risk is stronger associated with body composition than with body mass, and obesity can be subdivided into a group of centrally localized body fat, where much fat is stored in intra-abdominal, visceral depots, and a peripheral gluteofemoral subgroup. The former carries the majority of the risk of obesity related diseases (Bjørntorp & Rosmond, 2000).

### 5.3.1. Definition

Several working definitions of the MetS are being employed, thus complicating the comparison of prevalence and impact between studies. Most current reports within the field of psychiatry base their analyses on the definition proposed by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) (Expert Panel of Detection, 2001), or on the ATP III version revised by the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) in 2003 (Grundy *et al,* 2005). For establishing the diagnosis according to the AHA/ NHLBI definition of MetS, at least three out of five of the following criteria must be present: (1) FPG $\geq$ 5.6 mmol/l = 100 mg/dl, or on drug treatment for elevated glucose; (2) TG $\geq$ 1.7 mmol/l = 150 mg/dl, or on drug treatment for elevated TG; (3) HDL-C < 1.04 mmol/l = 40 mg/dl (men) and < 1.29 mmol/l

= 50 mg/dl (women), or on drug treatment for reduced HDL-C; (4) Systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mm Hg, or on antihypertensive drug treatment; and (5) Central obesity: waist > 102 cm = 40 in. (men) and > 88 cm = 35 in. (women).

### 5.3.2. Prevalence of the metabolic syndrome in patients with severe mental illness

The first report on a raised prevalence of MetS in schizophrenia was published by Heiskanen *et al (*2003). It was soon followed by others (Basu *et al,* 2004; Cohn *et al;* 2004). Although these pioneering studies were small-sized and suffering from the lack of reference groups, they opened up a new field of interest, by suggesting a 2-4 times raised prevalence of MetS among patients, and indicating a high occurrence at much younger ages than in the general population (Cohn *et al,* 2004). The issue was pursued in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study (Lieberman *et al*, 2005). Parallel to the publication of Paper I in the present thesis, McEvoy *et al* (2005) reported on baseline findings from 686 chronic schizophrenic patients in the CATIE Study, where the prevalence of MetS was over 35 % in males and over 50 % in females. At approximately the same time, Saari *et al* (2005) found that schizophrenia patients from the Northern Finland 1966 Birth Cohort Study had a 4-fold risk of MetS. In addition, the data indicated that risk was particularly increased in young individuals.

## 5.4. Introduction to the sub-studies

### 5.4.1. Risk across populations and the role of sociodemography (Paper I)

Life style related disorders, such as obesity, MetS, and type 2 diabetes are known to vary across continents, with much higher prevalences in the USA than in Europe (Balkau *et al*, 2002; Ford *et al*, 2002). At the onset of the present study, reports on CVD risk in psychiatric populations were scarce and predominantly based on American samples of chronic schizophrenia patients. On this background, we decided that a prevalence study of CVD risk factors in a more representative sample of Norwegian patients with SMI would be a good starting point for this thesis.

Inherent metabolic risk depends closely on biological variables such as age, sex, and ethnicity, while amenable lifestyle risk is linked to cultural and socioeconomic factors (Hu *et al*, 2004). CVD risk may change in the course of a few years with altered life style in any given population (Strand & Tverdal, 2004). As in the rest of the Western world, overweight, type 2 diabetes, and insufficient physical activity are increasing health problems in Norway (Midthjell *et al*, 1999; Graff-Iversen *et al*, 2007). Despite this worrisome fact, there has been a decline in cardiovascular deaths over the last four decades (Norwegian Institute of Public Health; Jenum *et al*, 2007). This is largely the product of two factors: important progress in medical care and intense campaigns to improve public health related behaviour. In the general population, these campaigns have been successful in reducing the rates of smoking, hypertension and high cholesterol levels.

However, public health information is known to be more effective with some sections of the population than others, and well educated individuals are the most likely to adjust their lifestyle according to recommendations from the health authorities. In Norway, the variation in health risk factors is larger within the capital of Oslo than among any other region of the country, reflecting a larger variation in educational levels, as well as in genetic, cultural, and socioeconomic conditions. We therefore wanted to compare CVD risk in a patient sample drawn from the city of Oslo, with reference data from the general population of the same geographical area within the same time span. A compelling question would be whether sociodemographic differences between the two cohorts could explain any differences found.

The choice of sociodemographic factors to investigate was based upon previous studies. In addition to age and sex, ethnicity is highly predictive of raised CVD risk (Chaturvedi, 2003), and increased prevalences of obesity and type 2 diabetes has previously been demonstrated in immigrant groups living within the urban society of Oslo (Jenum *et al*, 2005). As to socioeconomic differences, educational levels has previously been shown to impact upon health related behaviour in a more consistent fashion than income, resulting in a significantly lower morbidity and higher life expectancy among well educated individuals living in Norway. Finally, previous population studies have shown marital status to be of importance, and living single to be associated with a poorer lifestyle and higher CVD risk,

at least in males (Strand & Tverdal, 2004). On this basis we decided to include data on ethnicity, marital status and level of education as explanatory variables in our investigation, in addition to age and gender.

### 5.4.2. Cardiovascular risk in bipolar disorder versus schizophrenia (Paper II)

At the time when we started our investigation, there were few reliable reports on somatic risk factors in bipolar patients to be found, although cardiovascular mortality had been reported to be approaching that of schizophrenia (Harris & Barraclough, 1998; Angst *et al*, 2000; Ösby *et al*, 2001; Kupfer, 2005). Some authors had described elevated rates of obesity (Elmsie *et al*, 2000; Fagilioni *et al,* 2002; McElroy *et al,* 2002; Keck & McElroy, 2003) and diabetes (Cassidy *et al*, 1999) in bipolar disorder, and other reports on hypertension (Johannessen *et al*, 2006), and the MetS (Fagilioni *et al*, 2005; Yumru *et al*, 2006) were published in parallel to our enquiries. Most of the previous studies, however, were on highly selected samples, without normal reference groups; and only Johannessen *et al* (2006) had compared the risk prevalence in bipolar and schizophrenia patients. Interestingly, during the progress of our work, an excellent study was published, showing obesity to be significantly associated with mood disorders in a sample of nationally representative US adults, particularly in those segments of the population where the overall rates of obesity were lowest, such as young, highly educated, white females (Simon *et al*, 2006). In addition, depression was shown to increase the risk of developing insulin resistance and type 2 diabetes (Timonen *et al,* 2005; Enger *et al,* 2006).

Patients with bipolar disorder are generally less impaired, clinically, cognitively and socially, than patients with schizophrenia, and would therefore be considered more capable of adopting a healthy life style. Furthermore, antipsychotics, known to induce weight gain, are less widely used in this group of patients compared to patients with schizophrenia. Such circumstances should favor a more beneficial CVD risk profile in people with bipolar disorder. On this background, we decided to compare a representative sample of bipolar versus schizophrenia patients on the prevalence of CVD risk factors, as well as on sociodemographic variables, psychiatric symptom severity and drug use. In addition, both

groups were compared with a gender matched and age adjusted reference group from the general population of Oslo.

### 5.4.3. Metabolic side effects of antipsychotic treatment (Paper III)

Before and during the progress of our investigation, numerous prospective, randomized studies and register based population studies have reported on different liabilities to cause metabolic side effects among APs (Sernyak *et al,* 2002; Koro *et al,* 2002; Tandon & Gibson, 2003; McQuade *et al,* 2004; Zhang *et al,* 2004; Nasrallah, 2006; Olfson *et al,* 2006; Fleischhacker & Widschwendter, 2006). However, such differences have not been readily demonstrated in studies of patients receiving treatment as usual (Smith *et al,* 2005; Cohen *et al,* 2006; Remington, 2006). Actually, we found only one report linking a raised prevalence of the MetS to the use of a specific drug, namely CLZ (Lamberti *et al,* 2006). This study was clearly performed on a highly selected patient sample; and the investigators did not have access to a proper control group, but used only references to general population data.

Most previous investigations had focused on the obesogenic properties of SGAs, causing subjective distress and often leading to non-compliance with treatment (Weiden *et al,* 2004). Meta-analyses had shown CLZ and OLZ to induce more weight gain than other APs (Allison *et al,* 1999; Allison & Casey, 2001). However, this has not been consistently found in clinical treatment studies (Smith *et al,* 2005; de Leon *et al,* 2007). Other studies indicated that APs such as CLZ and OLZ, besides weight gain, could induce metabolic disturbances, in particular insulin resistance and glucose intolerance, independent of obesity (Newcomer *et al,* 2002; Henderson *et al,* 2005; Ader *et al,* 2005; Wang *et al,* 2006; Houseknecht *et al,* 2007; Sacher *et al,* 2007). The question of whether dyslipidemia could also be a direct effect of AP treatment had been much discussed, but was as yet unsolved (Meyer & Koro, 2004). To further elucidate these issues, we set out to compare the distribution of obesity and related metabolic parameters in a naturalistic sample of young outpatients on strict monotherapy with different AP agents, using currently drug free patients as a control group.

### 5.4.4 Hormonal dysregulation following antipsychotic treatment (Paper IV)

Increased appetite, has been proposed as a mechanism for AP induced weight gain and MetS, in addition to alterations in body composition, energy expenditure, and glucose metabolism, but the molecular pathways leading to such effects are not well understood (Zhang *et al,* 2004; Graham *et al,* 2005; Kim *et al,* 2007; Meltzer, 2007). Drug interaction with several neurotransmitter receptors has been hypothesized. Since APs have complex pharmacological actions and interact with virtually every type of biogenic amine receptor in the brain, a large number of candidate receptors have been proposed. In a study from 2003, Kroetze *et al* showed that the most robust predictor of a drug's propensity to induce weight gain was its affinity for the $H_1$-histamine receptor (H1R). APs with high H1R affinity are typically drugs reported to be obesogenic, such as CLZ and OLZ, while APs with low H1R affinity are those shown to induce minimal weight gain, such as ziprazidone and aripiprazole.

Kim *et al* (2007) recently demonstrated that CLZ and OLZ, through high H1R receptor antagonism, cause potent and selective stimulation of the intra-neuronal enzyme adenosine monophosphate (AMP)-activated protein kinase (AMPK) in the hypothalamus of rats, thereby blocking the action of the anorexigenic hormone leptin, with resulting hyperphagia and weight gain. The study also showed that CLZ reverses the suppressive effect of insulin on AMPK in the hypothalamus of research animals, causing central insulin resistance, which, besides obesity, has been proposed as the core pathophysiology of MetS (Reaven, 2002).

However, findings on the hormonal regulation of metabolism in rats are not directly applicable on humans. To further elucidate these questions, studies on real life patients are required, but hormonal resistance is not readily measured in clinical samples. Results from studies using surrogate measures need to be interpreted with care and a great variety of confounding variables must be accounted for. As in unmedicated healthy subjects, adiposity has been shown to be a main predictor of insulin resistance in AP treated patients, explaining at least one third of the variance in insulin sensitivity (Haupt *et al,* 2007). The same is probably true for resistance to leptin (Meier & Gressner, 2004). Samples should

thus be rigorously controlled for adiposity measurements, as well as for age, gender, and ethnicity, ideally also for smoking behaviour, exercise level, and diet. When comparing drug effects between treatment groups, these should be matched for psychiatric severity scores, and an unmedicated patient group should be included to control for the impact of SMI itself. Most previous naturalistic studies have failed to do so. In addition, the importance of co-medication with independent metabolic side effects has often been neglected.

Given all these obstacles, at the time of our investigation, only a few clinical studies had given indications of a direct effect of OLZ on insulin resistance in human subjects, independent of body mass (Newcomer *et al*, 2002; Henderson *et al,* 2005, Sacher *et al,* 2007). On the other hand, studies of APs on sensitivity to leptin had yielded conflicting and non-conclusive results (Melkersson & Hulting, 2001; Hägg *et al*, 2001; Haupt *et al*, 2005; Atmaca et al, 2003; Graham *et al*, 2005; Henderson *et al*, 2005; Smith *et al,* 2005; Hosojima *et al,* 2006). To further elucidate the issue of differential AP effect on resistance to insulin and leptin in humans, we chose to study variations in a variety of surrogate measures in a sample of patients naturally matched for most confounding variables, using unmedicated patients as a control group.

## 5.5. Aims of the thesis

***Overall aim***

The overall aim of the thesis was to gain more knowledge about CVD risk in patients with SMI, with emphasis on metabolic side effects of AP treatment.

***Subaims***

To investigate the prevalence and distribution of CVD risk factors in a sample of pharmacologically stable out-patients with SMI from the city of Oslo, and compare their risk profile to that of the general population. Furthermore, to examine whether differences in socio-demographic variables could explain differences in the risk profile between the patient and the reference group (Paper I).

To investigate the prevalence of smoking and metabolic disturbances in bipolar disorder and compare it with schizophrenia in a representative sample of patients under naturalistic conditions. Furthermore to compare the prevalence of CVD risk factors in each diagnostic group with the general population (Paper II).

To compare the distribution of obesity and other metabolic disturbances in a naturalistic sample of patients on OLZ (or CLZ) monotherapy with patients on monotherapy with other APs, considered less liable than OLZ and CLZ to induce weight gain, and with currently drug free patients. Furthermore to investigate if metabolic risk factors linked to any specific AP treatment appeared independent of body mass (Paper III).

To test the hypothesis that patients receiving OLZ had signs of increased resistance to leptin and insulin actions compared to patients receiving other AP agents, and patients receiving no AP treatment. Furthermore, to investigate if this coincided with signs of hepatic insulin resistance, as marked by a decreased level of SHBG, and whether any gender specific differences in hormonal regulation were present among treatment groups (Paper IV).

# 6. Materials and Methods

## 6.1. The Thematically Organized Psychosis Research (TOP) Study

The Oslo TOP Study is a large, multisite research study, carried out by the University of Oslo in joint collaboration with all four University Hospitals in Oslo on the basis of the specialist psychiatric services. Patients with SMI from all health care sectors of Oslo are included, the main diagnostic groups being schizophrenia and bipolar disorder. Inclusion of patients is ongoing. In this thesis, data are based on patients included in the study from start-up in October 2002 through July 2006. The study design is naturalistic, with a translational approach. Thus, a number of biological and clinical characteristics of SMI are investigated in order to gain more knowledge about the underlying pathophysiological mechanisms of disease.

The inclusion area covers practically the whole city of Oslo, with a total of 550.000 inhabitants, living in urban and suburban parts of the capital. The treatment system is catchment area based and publicly funded. Patients are referred from primary care. The core basis of the psychiatric specialist treatment system is subsector catchment area-based outpatient units, with the addition of acute, intermediate and long treatment units. Eligible patients were all those meeting study criteria and giving informed written consent of participation. The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study, and the biobank was approved by the Ministry of Health.

### 6.1.1. Subjects

Inclusion criteria for the TOP Study are broad, consisting of (1) being registered in the psychiatric services of any of the 4 University Hospitals in Oslo; (2) aged 18 to 65 years; (3) meeting the DSM-IV criteria for any major psychotic or bipolar disorder; (4) understanding and speaking a Scandinavian language; (5) having no history of severe head

trauma or neurological disease; and (6) having an Intelligence Coefficient (IQ) score over 70.

Patients are included mainly from the outpatient units of each health care sector, but also from intermediate and long treatment units. Patients in acute ward treatment are considered not currently capable of participation. These patients are instead approached after release from hospital**,** when their mental condition is stabilized. All participants are invited into the study by the clinician responsible for their treatment. Those willing to participate receive thorough information of the study aims and procedures from one of the PhD students responsible for the assessments, all of them trained psychologists or psychiatrists. The inclusion procedure itself is divided into several sessions and in total comprises eight hours or more of assessment, including clinical interviews, a physical examination and neuropsychological testing. The interviews take place partially at the patient's regular treatment unit, and partially at Ulleval University Hospital. Patients with problems using public means of communication are offered free transport by taxi.

Throughout the study period of this thesis, a total of 414 patients were included, 210 men and 204 women. Median age for both genders was 32 years, ranging from 17-67 years. Three hundred forty five (83 %) subjects were Caucasian, while, of the 69 (17 %) Non-Caucasians, the largest subgroup, 32 subjects (8 %), had origins from the Indian subcontinent. Of the entire sample, 51 % (121 men, 91 women) had diagnoses of schizophrenia, schizoaffective or schizophreniform disorder (here called *schizophrenia*), while 30 % patients (49 men, 76 women) had diagnoses of bipolar I, bipolar II, or bipolar NOS disorder (here called *bipolar disorder*). The rest of the sample, 19 % (40 men, 37 women), had diagnoses of psychosis NOS, delusional disorder, or severe depression with psychotic symptoms (here called *other psychotic disorders*). Comorbid DSM-IV diagnoses of abuse or addiction to alcohol/ illicit drugs were found in 24 % of the patients (60 men, 40 women), a figure corresponding fairly well with other studies, where drug abuse has been reported in 15-77 % of patients with psychotic disorders (Ringen *et al,* in press).

Duration of illness, estimated from first contact with the specialized psychiatric service, was in the range of 0-48 years for the entire sample, with a median duration of 3 years. At the time of assessment, 346 (84 %) of the subjects were outpatients, while 67 (16 %) subjects were hospitalized. Total PANSS scores of the entire sample ranged from 30-123, with a median value of 53, while symptom GAF scores ranged from 15-92, with a median value of 45, and function GAF scores ranged from 22-85, with a median value of 45. The general level of education was high, with a median of 13 years of completed schooling, ranging from 7-25 years. Neuropsychological assessments performed on subsamples of the entire cohort showed that mean IQ scores of study subjects were within the normal range (Vaskinn *et al,* 2007; Vaskinn *et al,* in press).

AP drugs were prescribed to 73 % (N=302) of the patients, and 19 % (N=78) received two or more different APs. Antiepileptic mood stabilizers were prescribed to 31 % (N=130), lithium to 7 % (N=29), and antidepressants were prescribed to 35 % (N=146) of the patients. As much as 11% (N=47) of the patients received no AP, mood stabilizing, or antidepressant agent. These figures correspond well with other studies estimating standard drug regimes given to Norwegian patients with major psychoses (Johnsen *et al,* 2004). Jonsdottir *et al*, reported, in a newly submitted study on the present sample, that out of 255 patients, 196 (77 %) had a 100 % self-reported adherence to medication. Of these subjects, 158 (81%) had serum drug concentrations within the reference range, or higher, while 34 (17 %) had serum concentrations below reference range, and only 4 (2 %) had non-detectable serum concentrations The authors concluded that adherence rates were unusually high compared to other naturalistic studies on outpatients with SMI.

### 6.1.2. Measurements

***Psychiatric assessments***

All assessments were made by a group of trained psychiatrists and clinical psychologists. Clinical interviews were performed, with additional information collected from treatment records to determine demographic factors, psychiatric history, medical history and current use of psychotropic medication, tobacco, alcohol and illicit drugs.

The Structured Interview for the DSM-IV Axis I Disorders (SCID-I) was used for diagnostic purposes (First *et al,* 1995). The SCID-I is a semi-structured interview, making use of all available information on the patient. In addition to direct information from the interviewees and the clinical staff responsible for treatment, the interviewers had access to the patient's complete clinical file. All interviewers received training in use of the SCID-I, based on the training program at the University of California, Los Angeles (Ventura *et al,* 1998). In addition, regular diagnostic consensus meetings were held, led by a well experienced clinical researcher in the field. To assess reliability, a random sample of 28 cases was drawn, stratified to include an equal number of cases from every member of the assessment team. Anonymous vignettes describing symptoms and development of the illness were then rated by two experts blind to the study ratings. Inter-rater reliability was deemed to be highly satisfying, with an 82 % overall agreement on diagnostic categories and an overall $\kappa = 0.77$ (95% C.I: 0.60-0.94).

Psychosocial functioning was measured by the Global Assessment of Functioning Scale (Endicott *et al,* 1976), and the scores were split into scales of symptoms (GAF-S) and function (GAF-F) to improve psychometric properties (Pedersen *et al,* 2007). The inter-rater reliability was good with an intra class correlation coefficient (1.1) = 0.86 for both symptom and function GAF scores (Shrout and Fleiss, 1979).

Psychiatric symptom ratings were done using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al,* 1987). Inter-rater reliability was satisfying, with intra class correlation coefficients (1.1) = 0.73, 0.73 and 0.71 for PANSS positive, negative and general scores, respectively. In addition, the Inventory of Depressive Symptoms Scale (IDS) (Rush *et al,* 1996) was used for assessment of depression severity level.

***Somatic assessments***

Physical examinations were performed immediately after the interview. Blood pressure (BP) was measured manually in a sitting position after resting, and body mass index (BMI: weight in kg/height in $m^2$) was calculated by asking patients about their height and weighing them on calibrated digital weights wearing light clothing but no shoes. Waist

circumference was measured midway between the lower rib and the iliac crest in the upright position using a non elastic tape.

Blood samples were drawn after an over-night fast of at least 8 hours and analyzed for fasting plasma glucose (FPG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides (TGs). All serum analyses were performed at the Department of Clinical Chemistry, Ulleval University Hospital, on an Integra 800 (Roche Diagnostics), using standard methods. Serum or plasma levels of insulin, leptin and adiponectin were measured with radioimmunoassay (Linco Research, Inc, St. Charles, MO, USA), serum cortisol by luminoimmunoassay, and Sex hormone binding globulin (SHBG) by immunoluminometric assay (Diagnostic Products Corporation, Los Angeles, CA, USA), all at the Department of Endocrinology, Aker University Hospital. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to assess insulin resistance (IR) on the basis of the known relationship between FPG and serum insulin concentrations (Mathews *et al,* 1985). The HOMA-IR was calculated by the following formula: HOMA-IR = [(fasting insulin (pmol/L) x FPG (mmol/L) / 135]. Serum concentrations of antipsychotic drugs were analyzed at the Department of Clinical Pharmacology, St. Olavs Hospital, Trondheim.

## 6.2 Reference material / the 2000-2001 Oslo Health (HUBRO) Study

The population based HUBRO Study was conducted in Oslo from May 2000 to September 2001 by the Norwegian Institute of Public Health in joint collaboration with the Oslo City Council and the University of Oslo. The aim of the study was to identify variables at the individual level to explain social inequality in health. The Regional Committee for Medical Research Ethics reviewed the study protocol and the Norwegian Data Inspectorate approved the study. All participants gave their written consent. More details about this study can be obtained from the Norwegian Institute of Public Health (www.fhi.no).

### 6.2.1. Subjects

All citizens aged 30, 40, 45, 59-60 and 75-76 years were invited to attend the screening station located in the city center. Of the 40,888 citizens invited, a total of 18,770 individuals (46 %) participated in the survey. To match the age span of the TOP Study, only individuals in the age group of 30 to 60 years were included as a reference group in the present thesis, 6879 men and 8307 women (Paper I & II).

### 6.2.2. Measurements

Information on age, gender, country of birth, and marital status was recorded from Statistics Norway (Oslo, Norway). All other information on demographic and health issue data was collected from questionnaires filled in by the participants. At the time of screening, a clinical examination was conducted according to a standard protocol. All participants were measured and weighed on electronic scales. BP was taken using an automatic device (DINAMAP, Critikon, Tampa, FL). Nonfasting venous blood samples were taken for TC, HDL-C, TGs and glucose. Serum analyses were performed by the same methods and in the same laboratory as for the TOP Study.

For the purpose of the present study we made use of the following demographic variables: age, gender, country of birth, country of birth of the parents, years of education, and marital status. We made use of the following self-reported health issue data: self-reported diabetes, use of diabetes medication, and daily smoking; and the following data from the clinical examination: BMI, BP, blood glucose and lipid levels.

## 6.3. Sub-studies sampling procedures

Details on the study sampling procedures are summarized in *Figure 1* below.

***Paper I:***

For the purpose of investigating the CVD risk prevalence in a representative sample of patients with severe mental illness, we compared data from all patients included into the ongoing Ulleval 600 Study by May 2005 (205 pharmacologically stable outpatients with

DSM- IV psychotic or severe affective disorders), with reference data from subjects of the same age-group in the 2000-2001 Oslo Health Study (15,186 individuals from the general population of the same area). Subjects were stratified according to age and gender and compared for ethnic background, level of education, marital status, and prevalence of risk factors. The Ulleval 600 Study was later integrated into the larger TOP Study.

***Paper II:***

For the purpose of comparing CVD risk factors in schizophrenia and bipolar patients, we excluded all subjects with other diagnoses from the main sample included into the TOP Study by December 2005. Schizophrenia patients (n = 163) and bipolar disorder patients (n = 110) were then compared on sociodemographic variables, psychiatric symptom severity measures, prevalence of smoking, and age adjusted levels of metabolic risk factors. Current use of psychotropic medication was described for both groups. Finally, risk factors in both groups were compared with reference data from the general population (15,186 individuals from the 2000-2001 Oslo Health Study).

***Paper III:***

For the purpose of investigating the amount of cardio-metabolic risk that could be attributed to specific antipsychotic treatment in a naturalistic sample, we excluded all patients who were not on strict monotherapy with one single AP agent, or unmedicated, from the main sample included into the TOP Study by July 2006. Study subjects were then divided into three groups according to actual treatment with OLZ or CLZ (N=80), monotherapy with any other antipsychotic (N=80), or unmedicated (N=82). Groups were adjusted for age and compared for prevalence of the metabolic syndrome and its components. Groups were further adjusted for body mass and compared for mean values of BP, FPG, and lipids.

***Paper IV:***

For the purpose of investigating whether signs of hormonal dysregulation could be attributed to OLZ treatment in a naturalistic cross-sectional sample, we excluded all patients who were not on strict monotherapy with one single AP, or unmedicated, from the main

sample included into the TOP Study by July 2006. In addition, CLZ treated patients were excluded for reasons of representativity. Study subjects were divided into three groups according to actual treatment with OLZ (N=72), monotherapy with any other AP (N=80), or unmedicated (N=82). Groups were adjusted for age and BMI, and compared for HOMA-IR, fasting concentrations of FPG, insulin, adiponectin, and cortisol. Gender stratified analyses were performed for leptin and SHBG.

## Figure 1.

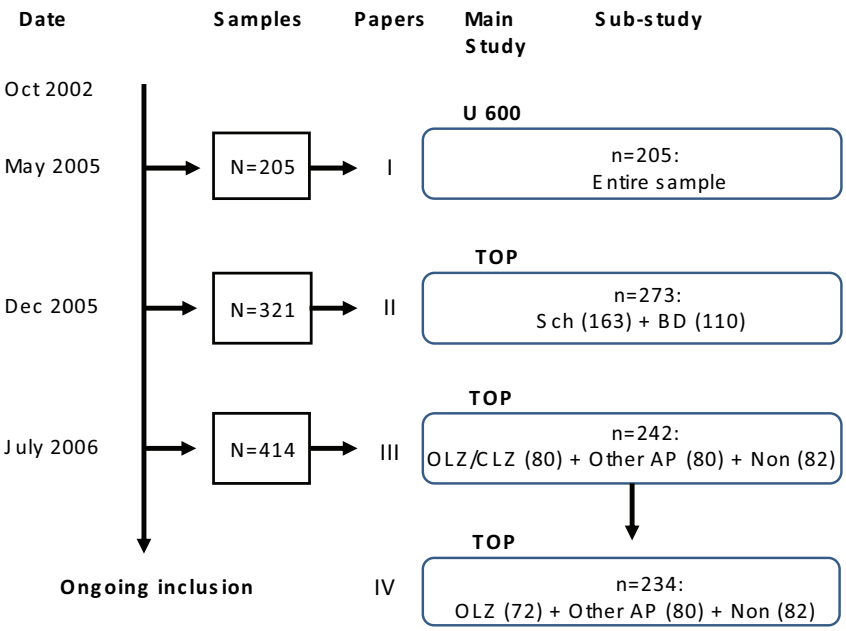


Figure showing the sampling procedure for the four individual sub-studies of this thesis. Abbreviations: U600: Ulleval 600; TOP: Thematic Psychosis Research Study; Sch: schizophrenia; BD: bipolar disorder; OLZ: olanzapine; CLZ: clozapine; AP; antipsychotics; No AP: currently unmedicated.

## 6.4. Statistical analyses

All analyses were performed using the Windows SPSS software package for Windows version 12.01-14.01 (SPSS, Chicago, IL). Descriptive statistics were represented as mean ± SD or proportions for observed values, and as mean (95% C.I.) for adjusted values. Categorical demographic variables were compared using the Chi-square test, and continuous demographic variables were compared using one-way analysis of variance and independent sample *t* tests. Pairwise comparisons were only made if the P values were ≤ .05 in the overall group effect F tests. Two-sided tests were used. Log transformations were performed prior to statistical analyses for data that were not normally distributed, but data were given as real numbers for clarity. Univariate analyses of covariance were used to compare outcome variables across groups when adjustments were needed for differences in age and BMI. The strength of the linear relationship between two parameters was calculated using the Pearson correlation coefficient (r). The significance level was generally set to $p \leq .05$.

In Paper I, men and women were compared separately, first by comparing values for all patients to all controls, secondly by stratifying each gender into matching age-groups and comparing them separately. To avoid type I errors caused by a large N in this sub-study we used an a priori significance level of $P < 0.01$. To control for the effects of multiple comparisons in the metabolic variables we also did Bonferroni corrections, i.e. dividing the P value with number of within-group comparisons. In Paper IV, Leptin and SHBG were analyzed after stratification for gender, because of the large, gender-specific heterogeneity in these variables.

# 7. Results

## Paper I:

Patients had an overall prevalence of CVD risk factors, such as smoking, obesity, hypertension, Low HDL-C and diabetes mellitus about twice that of the reference group. Hypertension was mainly due to increased diastolic BP in patients. Systolic BP did not differ significantly between the two cohorts. TC levels were only moderately elevated in patients. TGs and FPG could not be statistically compared, because fasting blood values were not available in the reference group. However, prevalences of high risk values, as well as mean values for TGs and glucose, although fasting, were higher than in the non-fasting reference group, with the exception of TGs in males. Patients aged 18 through 45 years had the highest level of risk factors when compared to the general population. There was no major difference in sociodemographic factors such as ethnic background or educational level between cohorts, although a significant higher number of patients were unmarried / living single.

In conclusion, the CVD risk profile in this sample of Norwegian outpatients was alarmingly high, particularly in young individuals, and could not be explained by socio-demographic factors alone.

## Paper II:

Patients with bipolar disorder had significantly higher levels of education, better social functioning, less psychiatric symptoms, and less use of AP medication than patients with schizophrenia. However, there was no significant difference in the prevalence of smoking, obesity, metabolic syndrome, or diabetes between diagnostic groups. Only mean levels of HDL-C was lower in schizophrenia ($p<0.001$), and systolic BP was higher in bipolar disorder ($p<0.05$). Both diagnostic groups had a prevalence of CVD risk factors about twice that of the general population.

In conclusion, the prevalence of CVD risk factors was very high, and approximately the same in bipolar disorder and schizophrenia.

### Paper III:

There was no significant difference among treatment groups in the prevalence of obesity, hypertension, or hyperglycemia. The age adjusted prevalence of MetS was 24 % in the OLZ/CLZ group, 16 % in the Other AP group, and 12 % in the No AP group. However, these differences did not reach statistical significance. Despite similar BMI, OLZ/CLZ treated subjects had a significantly higher prevalence of dyslipidemia (high TGs and low HDL-C) than unmedicated subjects. They also had higher mean values of TGs ($p=.003$), and lower mean values of HDL-C ($p<.001$). Patients treated with other APs had intermediate values.

In conclusion, adiposity and most other components of the MetS were equally distributed across treatment groups in this naturalistic sample. However, AP treatment, in particular with OLZ (and CLZ), was significantly associated with dyslipidemia, independent of body mass. This indicates a primary drug induced effect on lipid regulation which may be of importance in understanding AP mechanism of action. In addition, the findings have some important clinical implications, suggesting that lipid profiles should be monitored in all patients receiving AP agents.

### Paper IV:

Trend-level differences for HOMA-IR ($p=.051$), and significant differences for fasting concentrations of insulin ($p=.025$), adiponectin ($p=.017$), and cortisol ($p=.003$) were found across groups. OLZ treated subjects had the highest HOMA-IR and insulin concentrations, and the lowest adiponectin and cortisol concentrations. Females had significant inter-group differences for SHBG ($p=.001$) and leptin ($p=.005$), with OLZ treated subjects having the lowest SHBG and the highest leptin concentrations.

In conclusion, AP treatment, in particular with OLZ, was associated with alterations in several inter-related metabolic hormones, indicating insulin resistance independent of

obesity. Females had additional indications of resistance to leptin. The findings are in accordance with recent preclinical studies, suggesting that desensitizing to satiety signals may be a key mechanism for AP induced metabolic disturbances in humans.

# 8. Discussion

The main finding of the present studies was an alarmingly high prevalence in the study sample of CVD risk factors, including smoking, obesity, hypertension, diabetes, dyslipidemia, and the metabolic syndrome. Risk was particularly increased in young subjects, and similar in bipolar and schizophrenia patients. High risk could not be explained by sociodemographic factors or current use of AP drugs alone. However, dyslipidemia and signs of insulin and leptin resistance were significantly associated with AP medication, in particular with the use of OLZ. Females seemed to be particularly at risk for developing cardio-metabolic disturbances.

## 8.1. Discussion of results

### 8.1.1. Prevalence of cardiovascular risk factors in patients with severe mental illness

Our findings (Paper I) of an approximately two-fold increase in most CVD risk factors in patients with SMI compared to the general population are in accordance with other, recent studies (Heiskanen *et al,* 2003; Basu *et al,* 2004; Cohn *et al,* 2004; McEvoy et *al,* 2005; de Leon *et al,* 2005; Saari *et al,* 2005; Fagilioni *et al,* 2005; De Hert *et al,* 2006; Yumru *et al,* 2007). Investigators report on largely increased prevalences of MetS and daily smoking in psychiatric patients across the European and Northern American continents, despite differences in sample characteristics regarding sociodemographic and clinical status. The findings are in line with epidemiological research showing that mortality from CVD in SMI patients is increased, and that the differential mortality gap compared to the surrounding population is rising (Saha *et al,* 2007). The findings thus have important implications for clinical practice.

In agreement with other investigators, we also found that the relative prevalence of risk factors was highest in the youngest age group of patients (Paper I). The results correspond with the findings of Osborn *et al* (2007), that patients with SMI aged 18-49 years have a 3-

fold mortality risk from CVD compared with the general population, while, with increasing age, the relative risk flattens out. In addition, there were indications in our study, as in others (Allison *et al,* 1999[b]; Homel *et al,* 2002; McEvoy *et al,* 2005; Hakko *et al,* 2006), that females with SMI are at particular risk of developing obesity and metabolic disturbances (Paper I-IV).

One possible explanation for these findings may be that patients carrying the greatest risk have expired at a relatively young age, or young individuals may have been subjected to a more obesogenic lifestyle. Another possibility is that young patients, to a larger degree than older, have been treated with SGAs, in particular with OLZ, which for several years has been the most frequently used AP drug in Norway. Homel *et al* (2002) reported, in a study on overweight among schizophrenic versus non-schizophrenic individuals in a nationally representative sample of the US adult population, that from 1987-1996, BMI increased dramatically among women with schizophrenia ages 18-30, relative to their non-schizophrenic counterparts. This time period corresponds with the general introduction of the SGAs in the US. Interestingly, the same time trend was not found in males. The mechanisms underlying these findings remain unclear, but the authors speculate that metabolic side effects of the SGAs may be mediated by sex hormones.

Population based surveys have consistently shown that CVD risk factors vary with sociodemographic background, in that the wealthy and well educated, often predominantly Caucasian, segments of the population, have a healthier life style, lower health risk, and a longer life expectancy than others. In our study, no demographic divergence was found between the study and reference sample that could readily explain the large difference in CVD risk (Paper I). Other authors, prior to and in parallel to our enquiries, have reached similar conclusions. Saari *et al* (2005) found no association between the presence of MetS and demographic or clinical variables. Furthermore, Brown (1997), Brown *et al* (2000), and Osborn *et al* (2007) did not find any explicit link between increased mortality in the mentally ill and signs of social deprivation, such as poverty, civil status, employment status, or social class.

The authors of the CATIE Study concluded that MetS was more prevalent in schizophrenia patients than in any other group studied (McEvoy *et al,* 2005). However, there have been reports on a raised prevalence of obesity and MetS in individuals with bipolar disorder as well (Elmsie *et al*, 2000; Fagilioni *et a*l, 2002; McElroy *et a*l, 2002; Fagilioni *et al*, 2005, Yumru *et al*, 2007). As far as we know, our study (Paper II) was the first to directly compare subjects from these two diagnostic groups on all the components of MetS. Despite significantly better social functioning and less psychiatric symptoms in bipolar versus schizophrenia patients, the distribution of CVD risk was almost the same across groups. These findings strengthen the conclusion that sociodemographic variables are not central in explaining somatic risk factors in individuals with SMI (paper I). Furthermore, the findings indicate that mechanisms beside adverse effects of APs are involved, since the prevalence of risk factors was the same across groups, despite a substantial lower use of SGAs in bipolar subjects.

On the other hand, our findings are in line with recent population based studies showing mood disorders to be associated with obesity, type 2 diabetes and CVD (Simon *et al*, 2006; Engum, 2007; Fenton & Stover, 2006). One possible mechanism could be that chronic stress is related to severe affective disorders to a greater extent than to schizophrenia, causing alterations in the regulation of the HPA-axis that would induce metabolic disturbances, including abdominal obesity and the MetS (Bjørntorp & Rosmund, 2000; Cowen, 2002). A very strong association has previously been shown to exist between hypertension and increased HPA axis activity (Bjørntorp & Rosmund, 2000), indicating high levels of hypothalamic arousal. In accordance with one parallel study (Johannessen *et al*, 2006), we found systolic BP to be significantly higher in bipolar than in schizophrenia patients. This seems to support the hypothesis that perceived stress may be etiologically linked to metabolic disturbances in severe affective disorders.

In addition, there is accumulating evidence that feeding is not just a matter of energy homeostasis, but of emotional regulation (Saper *et al,* 2002; Kishi & Elmquist, 2005). In addition, disturbances in the circadian rhythm have been shown to effect metabolism in a negative way (Yin *et al,* 2007; Imaizumi *et al,* 2007). One could speculate that the

emotional dysregulation, and the disturbance in sleep pattern associated with bipolar disorder, may interfere with hunger and feeding mechanisms, leading to altered metabolism and obesity.

### 8.1.2. Metabolic side effects of antipsychotic medication

Besides BP, the only significant difference found between diagnostic groups (Paper II) was a lower level of HDL-C in schizophrenia subjects, most pronounced in women. The most plausible explanation for this finding was that medication differed greatly between the groups, with APs; OLZ in particular, being much more frequently prescribed to schizophrenia subjects. In addition, a large number of bipolar patients were currently unmedicated.

We explored this question by investigating the presence of metabolic risk variables in subjects on current monotherapy with OLZ (or CLZ) compared with other APs, using unmedicated patients as a control group (Paper III). Our findings were mainly in accordance with other reports published during the progress of our investigation, using a similar cross-sectional and naturalistic design. These studies investigated the prevalence of MetS (De Hert *et al,* 2006), diabetes and insulin resistance (Cohen *et al,* 2006), and hyperlipidemia (Smith *et al,* 2005; de Leon *et al,* 2007) across groups of patients treated with different APs. None of the investigators found significant differences in body mass, BP, MetS, or hyperglycemia across treatment groups. One explanation for this may be that clinicians tend to select drug treatment according to the somatic health risk profile of their patients, and avoid prescribing OLZ and CLZ in the presence of obesity, or any diagnosed metabolic disorder (de Leon *et al,* 2007).

Interestingly, one recently published, randomized and prospective study on drug naïve first episode patients, reported a substantial weight gain after 12 months of AP monotherapy in all subjects, but no significant difference was found between treatment with OLZ, risperidone, and haloperidol (Perez-Iglesias *et al,* 2007). The results seemed to mimic the observation by Planansky (1958), referring to the recently introduced drug chlorpromazine,

that all treatments showing effect in previously untreated, psychotic subjects are accompanied by weight gain.

On the other hand, our finding of significantly raised levels of TGs in OLZ treated subjects, independent of body mass, were in accordance with the results of Smith *et al* (2005) and de Leon *et al* (2007). However, none of these investigators reported on a decreased level of HDL-C, which was the most striking finding in our study. One reason for this discrepancy may be that co-medication with drugs other than APs were allowed in these studies, while subjects in our sample were on strict monotherapy. Another, equally or more important reason, could be that especially Smith *et al*, but also de Leon *et al*, had very few females included in their OLZ treatment group. Within our sample, low HDL-C was most pronounced in women, and after gender stratification and adjustment for both age and BMI, HDL-C in females was the only variable still significantly lower in OLZ treated than in unmedicated subjects (p=.006)

High levels of TGs combined with low levels of HDL-C are associated with insulin resistance and with increased risk for CVD (McLaughlin *et al,* 2003; Linsel-Nitschke & Tall, 2005; Semenkovich, 2006). This constellation, often named *atherogenic dyslipidemia*, is in normal subjects significantly correlated to visceral obesity. In our sample, this correlation was consistently found only in drug free patients. The findings indicate that some APs induce dysregulation of lipid metabolism independent of weight gain, and that females are most susceptible to this side effect of medication.

In humans, information from adipose tissue and nutrients is processed by the hypothalamus to maintain stable body weight through regulation of appetite, and to maintain stable levels of circulating glucose and lipids through regulation of the endogenous production in liver. This regulatory pathway, sometimes referred to as the “fat-brain-liver axis”, is mediated through a complicating interplay of hormones (Birkeland *et al,* 1993; Newcomer *et al,* 1998; Gabay & Kushner, 1999; Söderberg *et al,* 2001; Obici *et al,* 2002; Cnop *et al,* 2003; Cikim *et al,* 2004; Elmquist & Flier 2004, Schwartz & Porte 2005, Weinberg *et al,* 2006; Whitehead *et al,* 2006; Lam *et al,* 2007). AMPK, often described as a cellular fuel sensor, is

a central component in the energy homeostasis network of the "fat-brain-liver axis" (Minokoshi *et al,* 2004). Satiety signals, such as the hormones leptin and insulin, suppress the activity of AMPK in various parts of the hypothalamus, inducing appetite loss and downregulation of the endogenous production of nutrients. Lack of AMPK suppression has been shown to cause leptin resistance, with resulting hyperphagia (Minokoshi *et al,* 2004), as well as central insulin resistance, causing an increased endogenous production of TG-rich lipoproteins and glucose in the liver (Obici *et al,* 2002; Lam *et al,* 2007).

Throughout the progress of our investigation, preclinical and human studies had demonstrated that OLZ treatment influence on the regulation of metabolic hormones central to maintenance of energy homeostasis (Newcomer *et al,* 2002; Henderson *et al,* 2005; Ader *et al,* 2005; Albaugh *et al,* 2006; Richards *et al,* 2006; Sacher *et al,* 2007; Houseknecht *et al,* 2007). In addition, Kim *et al* (2007) had demonstrated, in a rat model, that these effects could be explained by OLZ affecting the regulatory function of AMPK in the hypothalamus. Encouraged by these findings we investigated if differences in a range of metabolic hormones would be present across treatment groups (Paper IV).

Our findings of high HOMA-IR, along with high levels of fasting insulin, and low levels of adiponectin in OLZ treated subjects, independent of body mass, are in accordance with previous studies (Newcomer *et al,* 2002; Henderson *et al,* 2005; Richards *et al,* 2006; Sacher *et al,* 2007), and indicate OLZ induced insulin resistance. This relationship is further strengthened by the correlations found between serum concentrations of OLZ and levels of HOMA-IR and insulin (Paper IV).

Our findings of high fasting levels of leptin in normal weight females, indicative of leptin resistance, seem more controversial. Leptin resistance has been proposed as one possible mechanism of OLZ induced hyperphagia and weight gain in a rat model (Kim *et al,* 2007), but previous clinical studies have yielded conflicting results (Henderson *et al,* 2005; Melkersson & Hulting, 2001; Hägg *et al,* 2001; Haupt *et al,* 2005; Smith *et al,* 2005). However, negative findings in some trials may have been due to a liberal use of co-medication allowed across treatment groups, and to the fact that very low numbers of

female subjects were included. Drugs other than APs could have independent effects on hormonal regulation, and leptin is known to be highly dependent on gender. Preclinical studies have shown that female rats are particularly vulnerable to hyperleptinemia and hyperphagia in response to OLZ treatment (Albaugh *et al,* 2006).

The present finding of increased leptin concentrations in OLZ treated females only may be due to the low age of most women in the TOP Study sample. Leptin and testosterone levels are known to correlate directly in premenopausal non-obese women (Söderberg *et al,* 2001), and this was also the case in our sample. We can only speculate that OLZ induced effects on androgens may contribute to a gender specific leptin resistance, which may contribute to the observation that female patients seem particularly vulnerable to develop obesity in response to antipsychotic treatment (Allison *et al,* 1999[b]; Homel *et al,* 2002; McEvoy *et al,* 2005; Hakko *et al,* 2006).

To our knowledge, no previous study has reported on decreased levels of circulating cortisol in association with OLZ treatment. Nevertheless, this finding is not surprising, since OLZ has a well documented sedative effect. However, low cortisol levels would be expected to protect against the development of insulin and leptin resistance (Newcomer *et al,* 1998; Bjorntorp & Rosmond, 2000). Our findings thus indicate that OLZ induced resistance to "satiety signals" occurs independent of body mass, and despite lower stress hormone levels.

Finally, to our knowledge, this is the first study suggestive of OLZ induced hepatic insulin resistance in humans, although this effect has been reported independent of weight gain in animal studies (Ader *et al,* 2006; Houseknecht *et al,* 2007). Our findings of a significantly increased TG/HDL-C ratio in OLZ treated patients, along with low SHBG and adiponectin levels, is indicative of an hepatic failure in suppressing the production of triglyceride-rich lipoproteins in the presence of elevated circulating insulin. Plasma glucose, on the other hand, will remain stable as long as the pancreatic production of insulin and the disposal of glucose by skeletal muscle remain adequate.

## 8.2. Discussion of methodological issues

### 8.2.1. Study and reference sample

The total clinical study samples comprised all patients included in the ongoing TOP Study at consecutive points of time (May 2005, December 2006, and July 2006). For the purpose of each sub-study, a lesser number of subjects were selected according to specific criteria. The number of individuals thus subjected to further investigation in each sub-study was: N=205 (Paper I), N=273 (Paper II), N=242 (Paper III), and N=234 (Paper IV). In Paper I and II, the study samples were compared with reference data from the population based HUBRO Study, comprising a total of 18,770 individuals. Only reference data for individuals within the age-interval of the TOP Study sample were considered (N=15,186).

***Representativity***

The inclusion area for the clinical TOP Study, as for the population based HUBRO Study, covered practically the whole city of Oslo. Psychiatric services in Norway are catchment area based and publicly funded. Outpatient clinics are equally distributed and offer a similar quality of care across all districts of the city, regardless of socio-economic and socio-cultural differences. Both study samples represented unselected cohorts, which were examined within a corresponding time interval of approximately four years, assuring concordance in time for variables susceptible of rapid changes within any given society.

Surveys on health equity are often hampered by selection bias due to low rates of participation among the invitees. In the HUBRO Study, the participation rate was 42.4 % in men and 49.3 % in women. As expected, information from the non-responders was insufficient to directly quantify the bias. However, non-responders could be traced, and an evaluation of the selection bias was made after linking public registers in Statistics Norway and the HUBRO Study (Søgaard *et al,* 2004). The authors found that response rates were positively correlated with age, level of education, total income, female gender, married status, born in a Western country, living in the outer city residential regions, and not receiving disability benefit. However, self-selection according to socio-demographic variables had little impact on prevalence estimates. Unhealthy persons attended to a lesser

degree than healthy individuals, but social inequality in health by different socio-demographic variables seemed unbiased.

As for the TOP Study, there was no possibility of tracing patients with relevant diagnoses who had not been included, since Norway, unlike other Scandinavian countries, does not have a national Hospital Discharge Register with available diagnoses. Due to the person data security act, information on invitees declining to participate was inaccessible. It was thus not possible to estimate the participation rate. However, some degree of selection bias must be assumed. Very impaired patients, lacking capacity of informed consent, would not be approached. It also seems likely that individuals suffering from severe cognitive deficits, massive negative symptoms, or paranoid ideation, would tend to decline participation, even when invited, or may not be capable of completing the inclusion procedures. In addition, the TOP sample was biased towards young subjects with a short duration of illness, since part of the total study focuses on first episode psychosis.

As one mean of estimating the representativity of the present clinical sample, we compared data from the TOP Study with accessible variables from the Ulleval 600 Health Care Study, a survey of all patients from the Department of Psychiatry, Ulleval University Hospital (constituting the largest and most heterogeneous health care sector of Oslo), conducted in the same time interval and comprising a total of 1002 subjects with ICD-10 F20-F39 diagnoses (psychoses and severe, affective disorders). Among these patients, 53 % (528) were male, and 47 % (474) were female. Mean (SD) age was 39.2 (12.8) years, and median age 38 years, ranging from 16-82 years. Mean (SD) symptom GAF was 40.2 (13.4), median value 38, ranging from 1-85. Mean (SD) function GAF was 40.3 (12.9), median value 39, ranging from 1-85. As described by Ringen *et al* (in press), the prevalence of illicit drug use in these two partially overlapping samples was almost identical (15.5 versus 15.2 %). However, TOP Study patients were younger (median age 32 versus 38 years), and had somewhat higher GAF scores than the Ulleval 600 Health Care Study sample (median values 45/45 versus 38/39).

From the descriptive data given in the Methods section, and from the comparison with the Ulleval 600 Health Care Study, we conclude that the TOP Study sample was representative of relatively young and ethnically homogenous individuals with verified diagnoses of psychotic or severe affective disorder, studied under real life conditions while receiving "treatment as usual". The majority of the cohort was outpatients, with a short duration of illness, a relatively high level of functioning, and very good adherence to medication. Furthermore, the sample had IQ-levels within the normal range, and an educational level equalling that of the general population (http://www.fhi.no). The confounding effects of hospitalization, long term treatment, and impaired cognitive and social functioning, were thus minimized, making comparison with a community sample more valid. In contrast to most other, recent studies in this field of interest (McEvoy *et al,* 2005; De Hert *et al,* 2006) reference data were collected from the general population of the same restricted geographical and socio-cultural area within a limited time-span, thus avoiding falsely enlarged differences between patients and controls because of the temporal trends towards more overweight and metabolic disturbances in the overall population.

***Ethical aspects and patients perspective***

Ethics had a special relevance in this project as it implied research involving sensitive personal information and use of biological materials from patients with severe psychiatric disorders. The potential ethical aspects of the research were paid attention to regarding its objectives, the methodology and the possible implications of the results. The central issue was that of informed consent and confidentiality – that participants knew how their information and blood samples would be used, and that measures to ensure confidentiality were secure.

The TOP Study was carried out in adult individuals, capable of giving informed consent. The clinical investigators in co-operation with the clinician in charge of treatment were responsible for assessing if individual patients were competent of giving consent. Individuals judged unable to consent were not included, nor were patients with below the

normal IQ range, or those not capable of speaking and understanding a Scandinavian language. No therapeutic clinical trials and no placebo therapy were proposed.

All data collection was performed with the approval of the Regional Ethics Committee (ref # 493-03-01179), and written informed consent was obtained prior to study participation. The following procedures were followed: Each participant had the study explained by a health professional (medical doctor or psychologist) and received a written explanation covering: the purpose of the study, the extent of investigations and interviews, personal information to be stored, how confidentiality would be maintained, and when the project would end (database deleted and blood samples destroyed). Patients were explicitly informed; both in oral and in writing, that participation in the study was voluntary, and that refusal to participate would have no consequence for their future treatment. They were also informed of their right to see all data registered on them, and have their data and blood samples destroyed at any occasion. The collection and handling of data were approved by the Norwegian Data Protection Agency (ref # 2003/2052) to preserve the personal privacy of the participants. In addition, the TOP database was inspected and approved by the Clinical Monitor at Ulleval University Hospital. All personal information was treated with the same confidentiality as required within the EU countries medical system, and the only persons with access to personal information will be health care professionals with a duty of confidentiality. All personal identifiers were removed, and only a code was used as identifier. This code was stored in similar security level as ordinary patient data at the hospitals. Most biological samples used for clinical biochemistry and hormonal analyses were sent directly to the laboratories using the same procedures and protocols as ordinary clinical samples. However, for some hormonal analysis, the biological samples were stored in the TOP Biobank, which is a registered research biobank approved by the Norwegian Ministry of Health (ref # 200403453).

Participants did not receive compensation for their participation, but in some cases transportation between the participants' home/work place and the sample collection facility was provided. People suffering from SMI are often concerned with somatic health issues related to weight, physical fitness, smoking, and the risk for developing diabetes and

cardiovascular disease. Through the TOP Study, we performed clinical interviews with a focus not only on psychiatric symptoms, but on the general medical situation of patients, including lifestyle and adverse effects of pharmacological treatment. All subjects benefited from a thorough clinical assessment, which was reported to the physician in charge of their treatment. In addition, participants had the opportunity to ask any questions they wanted about the study, about their specific disease state, or about health issues in general. Many participants profited from this opportunity, explicitly commenting that the focus on somatic issues within the study has been "meaningful and important", had made them feel "secure and well tended to", and inspired quite a few to make major improvements in their smoking, dietary and exercise habits. A large number of patients also expressed a need for better somatic screening and a closer follow up on medication and life style issues within the general health system. Throughout the study, we, as clinical investigators, were impressed by the interest, co-operability and tenacity of the participants, without which this research would not have been possible.

### 8.2.2. Assessments

***Psychiatric assessments***

The instruments employed for assessing psychiatric diagnoses, symptoms, and levels of functioning in the TOP Study are well recognized for use in clinical psychiatric research. The SCID-I interview is known to yield highly reliable diagnoses of Axis I disorders (Segal *et al,* 1994), and is considered to be the golden standard of diagnostic assessment. Likewise, the widespread use of the PANSS scale is based upon its excellent psychometric properties for assessing psychotic symptoms (Kay *et al,* 1987). The GAF Scale constitutes the axis V of the present DSM-IV diagnostic system, and has achieved worldwide status as a primary instrument for assessing change in psychiatric symptoms and functioning. Although its reliability in clinical settings has been questioned, it has proven highly satisfying in research situations (Vatnaland *et al,* 2007).

The TOP investigators were all clinically experienced psychologists or psychiatrists. They received ongoing supervision and participated in regular consensus meetings. A high standard was ascertained by senior researchers responsible for training and supervision, several of whom had previously taken part in projects involving an international network of co-workers, focusing on diagnosis and assessment of schizophrenia patients (Melle *et al,* 2004). In addition, all clinical investigators underwent an extensive and structured training program led by a well recognized American researcher within the field of diagnostics (Ventura *et al,* 1998). To assure inter-rater reliability of the test battery employed, testing was performed, yielding very good to excellent results.

***Somatic assessments***

Somatic examinations of TOP patients were performed by physicians according to a standard protocol, as described in the Methods section. The procedures were the same as for the HUBRO Study, with the exception for BP being measured manually in the TOP (mean value of three measurements after at least 10 minutes rest), and digitally in the HUBRO Study. Blood samples in the TOP Study were drawn by one specially trained project nurse. All blood samples were collected between 8.00 and 12.00 a.m., after at least eight hours of fasting. The HUBRO Study blood samples, on the other hand, were drawn at random time points, and were non-fasting.

The clinical chemical and hormonal analyses from the studies included in this thesis were performed at the Department of Clinical Chemistry, Ulleval University Hospital and the Hormone Laboratory, Aker University Hospital. The services of these laboratories are subject to regular internal precision and accuracy controls and both national and international quality controls in accordance with the recommendations of the Nordic committee on Quality Control of the Scandinavian Society for Clinical Chemistry. The departments participate in several external quality assessment schemes. The departments are working on accreditation and their quality systems are based on the general requirements for the competence of testing and calibrating laboratories.

### 8.2.3. Generalizability of findings

The city of Oslo is a modern, West European capital, with a social security system covering all inhabitants. The population is ethnically quite homogenous. All patients with SMI have the right to psychosocial and medical treatment free of charge. The great majority of individuals with psychotic disorders receive help from the public specialist outpatient clinics at one time or another. Most of these patients have the right to a disability pension and/or community housing. There are very few homeless people among them (Melle *et al,* 2000).

The first aim of this thesis was to compare CVD risk in mentally ill patients with the general population. We found that our setting would greatly minimize the risk of possible confounders seen in other studies, where chronicity (Cohn *et al,* 2004; McEvoy *et al,* 2005), limited sample size (Heiskanen *et al,* 2003; Saari *et al,* 2005), or single site inclusion (De Hert *et al,* 2006) could have hampered the results. Psychiatric and somatic assessments were shown to hold a satisfying standard, and the reference data were adequate. As estimates of increased risk are relative entities, we concluded that our findings would be generalizable to similar patient populations in other parts of the Western world. It seems likely that the increased CVD risk seen in this sample of relatively young and high functioning patients receiving an adequate standard of care and social security, would be even more pronounced in severely impaired patients living under less fortunate circumstances, as well as in patients of ethnic groups known to have a greater vulnerability for metabolic disturbances than Caucasians.

Our second aim was to compare CVD risk in patients belonging to one of the broad diagnostic categories of schizophrenia or bipolar disorder, which are both heterogeneous in their clinical appearance. The general level of functioning in bipolar disorder is usually better than in schizophrenia, although often highly state dependent. In the TOP Study sample, both diagnostic groups were included in a stable phase of disease, thus avoiding the confounding factors of stress intrinsic to acute psychotic or affective episodes. All subjects were nonetheless included from the same sites (predominantly outpatient clinics), implicating a continued need for specialist treatment. As expected, bipolar patients had

ratings for all background variables somewhere between the schizophrenia group and the general population. The comparison of the two groups was thus considered valid, reflecting the real difference in impairment normally found between individuals within these two diagnostic entities, and implicating that the findings of equal CVD risk was also generalizable to other settings.

The further aim of the present thesis was to investigate if treatment with any specific AP agent could be associated with metabolic abnormalities. Efficacy and side effects of APs usually tested in prospective, randomized studies, but these drug trials are often limited by highly selected samples, a short time span, and high rates of discontinuation. For more representative findings, naturalistic studies have been warranted. These, on the other hand, have often investigated chronic patients, where adverse lifestyle and lingering effects of previous medication could have influenced the results. Confounding factors such as non adherence, and co-medication with drugs other than APs, are rarely controlled for. In addition, there has been a striking lack of appropriate control groups in previous naturalistic reports.

Our investigation was performed on a representative sample of relatively young outpatients, under real-life conditions. From the total cohort, all subjects receiving AP treatment in monotherapy were selected, and divided into two subgroups: (1) All patients currently on OLZ (or CLZ), and (2) all patients currently on any other AP agent. The rationale for including several APs in the comparison group, despite a high degree of heterogeneity among them, was to increase statistical power. Furthermore, because of a lesser propensity to cause weight gain, they are often used as alternatives to OLZ in clinical practice. Subjects treated with co-medication of other drugs known or suspected to induce weight gain were not considered. The rationale of this procedure was to avoid the confounding effects of co-medication, which usually hamper naturalistic studies. In addition, all patients not currently receiving any drug treatment were uses as a control group, to rule out, as far as possible, the effects on metabolism of the disease itself. All subjects (except two) had been on their present medication regimens, or unmedicated, for at least 4 weeks, and adherence was controlled for by measurements of AP serum concentration.

### 8.2.4. Strengths and weaknesses of the studies

The studies included in this thesis had several strengths. The work was financially supported by public grants and was independent of sponsorship from the pharmaceutical industry. A naturalistic design was chosen, with a multi-site approach, and broad inclusion criteria, permitting us to gather information on a representative sample of individuals receiving "treatment as usual". The study had sufficient power to obtain statistically significant answers to clinically important questions, also after stratification for gender. The sample was well characterized, and reliability testing was performed for all central items. Subjects were relatively ethnically homogenous and overall young, with a short duration of treatment and a high general level of functioning, thereby reducing the confounding effects of ethnicity, long term hospitalization, and chronic disability. Moreover, subjects were generally in a stable phase of disease, limiting the uncertainty of whether findings should be ascribed to "state versus trait". Most subjects were on stable medication, and adherence was ascertained by measuring serum concentrations of all psychotropic drugs prescribed and of interest to the study. Complete medication history was obtained for practically all participants, thereby minimizing the confounding effects of previous medication.

In addition, reference data were collected from the general population of the same restricted geographical and socio-cultural area within a limited time-span, thus avoiding falsely enlarged differences between patients and controls because of the temporal trends towards more overweight and metabolic disturbances in the overall population. The HUBRO reference material thus had obvious advantages as compared to most other parallel investigations, including the CATIE Study.

However, the studies had some weaknesses. The cross-sectional design was not fit for drawing conclusions about causality, and the sample was not large enough for doing elaborate analyses on subgroups of interest. In addition, waist circumference was not obtained for the first 200 patients included in the TOP Study. Waist circumference is generally considered a better measurement for central obesity than BMI, and thus a stronger indicator of elevated CVD risk, particularly in women. Waist circumference is also one of

the AHA/ NHLBI criteria for MetS. We were obliged to use BMI as an alternative obesity measure for the whole sample in Paper I, and BMI as an alternative measure for part of the sample in Paper II-IV. As a consequence of this, prevalences of obesity and MetS were probably underestimated in our studies as compared to others, particularly for women. Furthermore, the lack of fasting blood samples in the HUBRO material hindered us from properly comparing TG and FPG between the clinical and the reference sample, and we did not have access to reference data for prevalences of MetS in the general population.

All substudies would have profited from direct information on important lifestyle issues, such as diet and physical activity. Instead, epidemiological data were used as indirect indicators of lifestyle in Paper I-II. In Paper III-IV, both treatment groups and controls were made up of patients with SMI, who were similar in clinical psychiatric characteristics, thereby minimizing lifestyle differences due to the disease state itself. An additional weakness of Paper II was the lack of data on previous psychotropic medication. This was, however, compensated for in Paper III-IV.

## 8.3. Clinical implications

The findings have some important clinical implications. First of all, CVD risk should be taken seriously for all patients suffering from SMI. In Norway today, a systemic separation exists in the provision of public mental health and general health care, thereby posing a barrier to accessing primary medical services (Levinson Miller *et al,* 2003). Hence, psychiatric personnel of all categories must be aware of the somatic risk involved in severe mental disease. Alongside standard psychiatric treatment, there should be a much stronger focus on lifestyle interventions, including smoking cessation programs, dietary counselling, and physical activity. These issues need to be effectively addressed from the patient's very first contact with the specialist psychiatric services. As young individuals seem to be carrying the largest amount of CVD risk, prevention should be given high priority. In addition, a joint effort is necessary to make detection and treatment of somatic risk factors and illness more available to psychiatric patients. Since public mental health services are clearly underserved concerning medical expertise, general community practitioners must be included in the assessment, monitoring, and treatment of high risk individuals.

When choosing AP medication, it is important to balance clinical gain against unwanted side effects, particularly for long term treatment. Somatic history and family anamnesis should always be taken prior to instigation of antipsychotic medication. In addition, physical exams should be performed, including measurement of weight, waist circumference, BP, and fasting blood tests. After instigation, patients should be carefully monitored and new exams performed on a regular basis. There are today no official logarithms for monitoring of physical health in SMI patients in Norway. Standardized recommendations are clearly needed. It must be underscored that obesity as the sole parameter of metabolic disturbances not sufficient. Our data clearly demonstrate that dyslipidemia, hypertension and insulin resistance are equally important risk factors, also in patients who maintain normal weight. We argue that regular monitoring is needed for all SMI patients, regardless of diagnosis, medication, and body mass.

In addition, our findings indicate that female patients are particularly at risk for developing obesity and diabetes as a complication to SMI, and that they may be more susceptible than men to the metabolic side effects of antipsychotic treatment. Women's health should therefore receive a renewed focus also within psychiatry, and special care taken when treating women with psychotropic medication.

## 8.4. Implications for further research

The increase in metabolic abnormalities found in patients with SMI cannot be ascribed to side-effects of SGAs alone. There is convincing evidence that disease specific factors other than medication are involved. Further studies are clearly needed to elucidate a possible covariance in the genetic susceptibility for developing SMI and metabolic disturbances. Since the heredity of both conditions is complex and must involve genes on several different loci, genome-wide studies on large scale samples are warranted.

There is previous evidence that the prevalence of type II diabetes is increased in schizophrenia subjects as well as in their otherwise healthy relatives (Mukherjee *et al,* 1989). On the other hand, type I diabetes has recently been shown to be inversely associated with schizophrenia (Juvonen *et al,* 2007). An interesting finding in our sample was the

exceedingly high prevalence of diabetes mellitus in women with bipolar disorder, although not conclusive because of small numbers. Of bipolar females, 8.6 % (5/61) had diagnosed diabetes, with 4.9 % (3/61) being type 1. Epidemiological, register based studies should be undertaken to examine the prevalence of type I diabetes in bipolar disorder. An interesting hypothesis is that a joint susceptibility for type I diabetes and psychosis may modify the phenotype of the mental disorder in a more affective direction, particularly in women. Hence, this is also an issue of interest for genetic investigation.

The issue of gender clearly needs to be further investigated. There are indications throughout our study, as well as in previous and parallel reports (Homel *et al,* 2002; Seeman, 2004; McEvoy *et al,* 2005; Hakko *et al,* 2006) that females with SMI are more at risk than males of developing overweight and other metabolic disturbances. This may be the result of a gender specific susceptibility to AP related side effects, perhaps in combination with other factors (genetic, hormonal, or environmental). Until recently, women's health has not been properly focused within psychiatric research, and clinical guidelines have often been based upon findings in predominantly male samples. There is an urgent need for prospective studies with sufficient power to investigate the effect of gender on somatic risk factors in psychiatric populations.

Hormonal regulation is an important topic in elucidating the molecular basis of metabolism, included drug induced side effects. Recently, there has been large progress in the understanding of how metabolic homeostasis is maintained. However, there are important obstacles to the investigation of centrally regulated processes in humans, and findings are mostly based on preclinical studies. However, since there is evidence that hormones involved in the "fat-brain-liver" axis may play a role in the metabolic abnormalities associated with SMI, a first step should be to compare concentrations of these hormones in representative psychiatric and healthy samples, matched for most possible contributing variables, such as age, gender, ethnicity, and body mass composition.

Metabolic homeostasis has been shown to be coordinated by circadian rhythms in plants and animals (Yin *et al,* 2007; Imaizumi *et al,* 2007). A fascinating new area of research

would be to study whether the sleep disturbances often associated with SMI, and in particular with bipolar disorder, could be linked to the development of hormonal dysregulation and metabolic disturbances. In order to do so, one would ideally need a well characterized sample of patients undergoing the different stages of bipolarity, and, if possible, followed prospectively from onset of their first affective episode.

To further elucidate the mechanisms of how different APs effect metabolic regulation, studies are needed in medication naïve first episode patients. A broad variety of parameters should ideally be measured at baseline, and after stabilization on AP monotherapy. In addition to investigation of FPG, lipids, hormones, and anthropometric variables, RNA from blood cells should be collected for microarray analysis, since there are indications that APs activate the expression of lipid biosynthetic genes in human cells, both in vitro and in vivo (Ferno *et al,* 2005; Ferno *et al,* 2006; Vik-Mo *et al,* in press). Parallel ratings of psychiatric symptom must furthermore be performed to investigate the hypothesis that weight gain and clinical effect on psychotic symptoms may somehow be related (Planansky, 1958; Procyshyn *et al,* 2007).

# 9. Conclusions

- Norwegian patients with SMI had an alarmingly high prevalence of CVD risk factors compared to the general population.
- Young patients (18-45 years) had the largest relative increase in CVD risk.
- Females had a particular high prevalence of obesity and diabetes.
- The increase in CVD risk factors could not be explained by socio-demographic factors alone.
- The increase in CVD risk factors was approximately the same in bipolar disorder and schizophrenia.
- Antipsychotic treatment, in particular with OLZ (and CLZ), was significantly associated with dyslipidemia, independent of body mass. The findings were most pronounced in females. Other components of the MetS were not significantly associated with any particular antipsychotic agent in this naturalistic setting.
- Antipsychotic treatment, in particular with OLZ, was associated with alterations in several inter-related metabolic hormones, indicating insulin resistance independent of obesity. Females had additional indications of resistance to leptin.

# 10. Errata

The printed version of this thesis is a reprint of the originally submitted thesis to the University of Oslo. One additional paper has now been published; Paper III in Journal of Clinical Psychopharmacology.

The following changes (seen **in bold)** have been made:

**1) Thesis**
Chapter 2. List of papers:
Paper III: Correct reference is **J Clin Psychopharmacol 2008;28(2):132-137.**

**2) Paper II**
Methods section, page 918, paragraph 3, is written "intraclass correlation coefficients = 0.86, df 1.1, for both symptom and function GAF scores". This is not correct, and should be substituted by ICC (1.1), referring to the first of six intraclass correlations described by Shrout & Fleiss (1977). The first number 1 means that the actual raters are considered as one sample of possible raters, while the second number 1 means that the reliability of single scores is assessed (in contrast to the mean of the scores by several raters). This has nothing to do with "degrees of freedom".

**3) Paper III**
a) Results section, page 134, Figure 1:
**OLZ**/CLZ, n = 80. ***P < 0.01, †P ≤ 0.001.**
Last line, legend: "…Other AP, patients treated with monotherapy of any other AP; **No AP, drug-free patients.**"

b) Results section, page 135, paragraph 1:
Finally, TG/HDL-C was significantly higher in group OLZ/CLZ **versus group No AP** (p<.001) and in group Other AP versus group No AP (p<.05).

c) Reference section, page 137, reference 35:
**WHO Collaborating Centre for Drug Statistics Methodology.** ***Guidelines for ATC classification and DDD assignment 2007*****. Norwegian Institute of Public Health. Oslo, 2006.**

**4) Paper IV**
Methods section, page 12, paragraph 1:
HOMA-IR = [(fasting insulin (**pmol/L**) x FPG (mmol/L) / 135].

Oslo, July 2008
Astrid B. Birkenæs

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